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08/644,289	05/10/96	KULESZ-MARTIN M	RPP:135D-US

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/644,289	Applicant(s) Kulesz-Martin
	Examiner Yvonne Eyler	Group Art Unit 1642

☒ Responsive to communication(s) filed on *May 14, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 3-6, and 8-19* is/are pending in the application.

Of the above, claim(s) *12-14* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 3-6, 8-11, and 15-19* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *14, 15*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 1, 3-6, and 8-18 are pending in the application. Claims 12-14 have been withdrawn from further consideration. Claims 1, 3-6, 8-11, and 15-18 are under consideration.

Claim Rejections Withdrawn:

3. The rejection of Claim 15 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn.

Claim Rejections Maintained and New Grounds of Rejection:

4. The rejection of Claims 1, 3-6, 8-11 and 15 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained and newly applied to claims 17 and 18 which depend off rejected claims 1 and 5 but do not clarify the issue.

Applicant indicates that the rejection is not understood. Applicant states that the word "active" is being missed or misunderstood and lack of the C-terminal regulatory domain renders p53as always "active." Applicant also indicates that the word "functionally" is being misunderstood and is intended to include only "growth regulatory" function as stated on pages 2

and 3 of the specification. Applicant has amended the claims to limit to "growth control" thus eliminating inclusion of any other aspects of functionality, such as antigenic functionality which is different from growth regulatory functionality. Applicant further argues that cellular function of p53 is known in the art.

Applicants arguments have been considered but are not found to be persuasive. The addition of language limiting the function of p53as and p53 to growth regulation equivalent to active p53 does not clarify the metes and bounds of the claimed molecule because definitive activities and properties or levels of activities and properties indicative of functionally equivalent growth regulatory activity are not provided. Key to this indefiniteness in the term "active p53" and its definitive properties. Applicant states that p53as lacks a C-terminal domain and hence is always "active." This is reflected in the specification at page 3 which discloses that p53as differs from p53 only in lacking the C-terminal negative regulatory domain which renders p53 inactive in some cellular environments. The specification also states that "the modified products will act the same as active p53 protein" but does not disclose what "acts" are definitive of active p53 protein and which acts serve to identify modified products as "acting the same." There is, however, no disclosure defining what activities or what level of activity identify p53 as "active" in growth regulation and thus facilitate determination of equivalent function. The specification also states on page 2 that p53as is essentially identical to "normal growth controlling p53" but does not define "growth controlling" activity. P53 plays a role in many cellular growth processes, including transcription, DNA repair, genomic stability, senescence, cell cycle control, and apoptosis (Harris.

J. Nat. Cancer Inst. Vol. 88, pages 1442, 1996). Applicants arguments and the disclosure of the specification are directed to regulating the function of DNA specific binding by the negative regulatory domain but do not address any other "growth controlling activities" definitive of "active" p53. Thus, given the complex role that p53 plays in many different cellular growth processes, it is not clear what properties, activities, or levels thereof, are definitive of functional equivalency.

5. Claims 16 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Both claims 16 and 19 recite a "portion of the peptide SEQ ID NO:1" for which the metes and bounds of the claimed portion cannot be determined. There is no guidance regarding what constitutes a portion. It cannot be determined what is considered to be a portion of SEQ ID NO:1 and what is not.

6. The rejection of Claims 1 and 5 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained and newly applied to dependent claims 3, 4, 6, 8-11, and 17 which incorporate the contents of claims 1 and 5.

Applicant argues that the specification teaches that the only differences between p53 and p53as are in the C-terminal 50 amino acids and that an epitope unique to p53as may be

incorporated within those final amino acids. Applicant further argues that one of skill in the art would be capable of selecting an unique epitope for inclusion at the terminal end of p53as. Applicant cites page 2 in support.

This argument has been considered but is not found to be persuasive. Modification to the C-terminal 50 amino acids does not contemplate or specifically teach epitopes. The disclosure on page 2 relates only to the requirement that p53as differ from p53 at the C-terminal 50 amino acids, but does not disclose epitopes within the 50 C-terminal amino acids which give rise to antibodies specific to p53as. While the only location for differential binding would likely be derived from these 50 C-terminal amino acids, there is no disclosure regarding the creation of epitopes (either linear or conformational) unique to p53as as instantly claimed. Disclosure of antibodies which specifically bind to p53as does not provide support for the epitopes to which the antibodies bind.

7. The rejection of Claims 1, 3-6, 8-11, 17, and 18 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

Applicant argues that it is clearly taught that the final 50 amino acids may be truncated to remove the negative regulatory domain from p53 and obtain a perpetually active p53, i.e. a p53as. Applicant further argues that an identifying epitope can clearly be added to the final 50 amino

acids of the truncated p53 and then addresses that one of skill in the art would know what type and size of epitope to incorporate.

These arguments have been considered but are not found to be persuasive because they are not commensurate in scope with either the claimed invention or the teachings of the specification.

The claimed invention is drawn to plasmids and vectors containing cDNA which encodes a protein that is different from p53 within the final 50 C-terminal amino acids so as to lack a negative regulatory domain. The protein is further characterized as being "functionally equivalent in growth regulation to active p53" and to possess a unique epitope.

The specification on the other hand discloses plasmids containing naturally occurring p53as which differs in 17 C-terminal amino acids and is truncated by 9, the result of alternative splicing of intron 10 or a synthetically generated p53as which consists of wildtype p53 up to residue 1039 and p53as from 1039-1059.

The specification does not provide sufficient guidance with regard to the scope of the claimed invention which encompasses any p53 molecule which differs in any way in the 50 C-terminal amino acids so as to disrupt the negative regulatory domain and to gain a unique epitope. The functional limitation does not remedy because one of skill would not be able to identify proteins which are functionally equivalent as the term is vague and indefinite as discussed supra. Further, the specification, and Wu et al. (IDS, paper # 14) would indicate that the instant p53as is

not functionally identical to "active" p53 as it is apparently is active in a different phase of the cell cycle indicating a distinct physiological function.

Further, applicants arguments are directed only to enablement of truncation which remove the negative regulatory domain or to the incorporation of epitope tags into the C-terminal 50 amino acids, the latter of which is not set forth in the specification as filed and constitutes new matter as set forth above. The scope of the claimed invention is drawn to p53 proteins with **any** difference in the 50 C-terminal amino acids. As made of record, there is insufficient guidance regarding the location (within the 50 C-terminal amino acids) of truncations or any other modifications that would result in a protein functionally equivalent to active p53 with a unique epitope. There is also insufficient guidance regarding the extent of truncations or any other modifications within the 50 C-terminal amino acids that would predictably result in a protein functionally equivalent to active p53. Further, as discussed supra, it is not clear what constitutes a functionally equivalent p53as protein. There are two very similar examples of p53as proteins, one naturally occurring which differs in 17 C-terminal amino acids and is truncated by 9 from alternatively spliced intron 10, the other a synthetically manufactured version of wildtype p53 with the 50 C-terminal amino acids replaced by those of naturally occurring p53as. There is insufficient guidance regarding any other species of p53as having any difference and retaining "functional equivalency" and gaining an epitope. There is also insufficient objective evidence that p53 proteins with any difference in the 50 C-terminal amino acids would predictably retain "functional equivalency" and be considered and identifiable as p53as proteins. As of record, the amino acid

sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be deleted and substituted within a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Furthermore, the activities which determine "function" are not clearly set forth or claimed as discussed supra, nor are the structural/functional relationships which maintain definable functions set forth. Therefore, the predictability of functional equivalence, elimination of negative regulation, and gain of unique epitopic properties as a result of any truncation and substitution within the C-terminus as not been established. Thus, while recombinant techniques are available and known in the art, it is not routine in the art to screen large numbers of substituted proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. It is maintained that it would require undue experimentation by one of skill in the art to practice the invention as claimed without further guidance from the instant specification.

8. Claims 16 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for plasmids or viral vectors containing SEQ ID NO:1, does not reasonably provide enablement for plasmids or viral vectors containing any portion of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex Parte Forman,* (230 USPQ 546 (Bd Pat. App. & Int. 1986)).

The specification discloses SEQ ID NO: 1 which is the region of intron 10 that is alternatively spliced in p53as. This region is unique to p53as and contains portions (albeit unidentified) that are recognized by p53as specific antibodies. The instant claim, however, is drawn to vectors containing any portion of SEQ ID NO: 1 without definition of the portion such that one of skill would be enabled to identify if they were in possession of a portion or not. The instant claim, and specification, also does not supply any definitive function of a portion sufficient to enable one of skill to make and identify a portion or to use the portion. The courts have taught,

> " [T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " In re Wright , 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); see also Amgen Inc. v. Chugai Pharms. Co. , 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); In re Fisher , 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (" [T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."). Whether making and using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries. See In re Wands , 858 F.2d 731, 735, 736-37, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). [emphasis added]

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1001 (CA FC 1997)

Thus, the specification is not found to be enabling, absent undue experimentation, to both make and use the instant portions of SEQ ID NO: 1 commensurate in scope with the claimed invention.

9. Claims 1, 3-5, 8-11, 17 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolf et al (IDS; Mol. Cell Biol. 5:127-132, 1985) or Arai et al.(IDS; Mol. Cell Biol. 6:3232-3239, 1986).

Both Wolf et al. and Arai et al. disclose plasmids and viral vectors containing a cDNA sequence that encodes a p53as protein.

Applicant argues that pM-8 is a clone, not a plasmid and that there is no disclosure or suggestion to insert the cDNA of Wolf et al. or Arai et al. into a plasmid or viral vector. Applicant also argues that there is no purpose, or different purposes suggested for use of the plasmids and that Wolf et al. and Arai et al. do not isolate the protein.

These arguments have been considered but are not found to be persuasive. First it is noted that the instant claims are not drawn to isolated protein, but to vectors containing cDNAs and thus isolation of protein is not necessary for the prior art to anticipate the instantly claimed invention. Further, intended use does not distinguish the plasmids of Wolf et al. and Arai et al. from those instantly claimed, because a composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982). Further, pM-8 is taught by

Wolf et al. to be a specific clone from a mouse cDNA library, made by ligation of cDNA into the EcoRI site of lambda gT10 which is a viral vector. Thus, pM-8 appears not to be a plasmid, but is rather a viral vector containing a cDNA sequence encoding a p53as. Wolf et al. subclone the cDNA insert encoding the p53as into puc13, which is a plasmid. Thus, Wolf et al. disclose both plasmids and viral vectors containing cDNA encoding a p53as. Similarly, Arai et al. disclose the pM-8 viral vector containing cDNA encoding a p53as. Arai et al. subclone the insert into pSP65 to generate a plasmid containing cDNA encoding a p53as.

The references supplied by applicant, Kulesz-Martin et al. and Wu et al. teach that the alternatively spliced cDNA of Wolf et al. and Arai et al. is not a wildtype p53as, but rather a mutant p53as. Applicant argues that therefore the instant invention is distinct from that taught by Wolf et al. and Arai et al. because mutant p53as would not be identical to p53 as is instantly claimed. This is not found to be persuasive because the instantly claimed plasmids and vectors are not limited to only wildtype p53as, but rather encompass any p53as. The limitations that the p53as be functionally equivalent in growth regulation to active p53 and be only different in the 50 C-terminal amino acids do not distinguish the claimed invention from that of Wolf et al. and Arai et al. The p53as of Wolf et al. and Arai et al. differs from the genomic clone only in the 50 C-terminal amino acids. The p53as of Wolf et al. and Arai et al. functions equivalently to the comparable genomic p53. That the genomic p53 is a mutant rather than wildtype p53 does not render it inactive in cell growth regulation, especially given the indefiniteness of the term as discussed supra. Thus both Wolf et al. and Arai et al. anticipate the invention as broadly claimed.

10. Claim 6 is are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolf et al (Mol. Cell Biol. 5:127-132, 1985) or Arai et al. or Arai et al (Mol. Cell Biol. 6:3232-3239, 1986) as set forth above regarding claims 1, 3-5, 8-11, 17 and 18 in view of Lee et al (IDS; EP 529160).

Wolf et al. and Arai et al. set forth as detailed above but do not teach baculovirus vectors containing the p53as cDNA. As made of record in the Office Actions of 2/10/99 and 10/15/97, Both Wolf et al. and Arai et al. suggest the need for further investigation of the role of p53as proteins in malignancy (See Wolf et al. page 131 and Arai et al. page 3238) while Arai et al. further teaches that the availability of cloned cDNA facilitates further investigation (page 3238).Both Wolf et al. and Arai et al. teach the desirability to further elucidate the properties of p53as protein.

Lee et al., as made of record in the Office Actions of 2/10/99 and 10/15/97 teaches the use of baculoviral vectors to produce large quantities of protein. Lee et al. teaches the importance of and the advantages of a mechanism to obtain intact, biochemically active protein in large quantities to advance investigation of the properties of that protein. (See page 2, lines 40-45). Lee et al. teach the cloning of cDNA into viral vectors to accomplish this advantage. Thus, not only does Lee et al. teach the technical feasibility of a reasonable expectation of success, Lee et al. also teaches a motivation to do so, i.e. to obtain large quantities of protein for investigation.

Applicant argues that there is no teaching or suggestion in the art to make plasmid constructs and there is no suggestion or motivation to insert p53as of Wolf et al. and Arai et al. into a virus or a reasonable expectation of success.

These arguments have been considered but are not found to be persuasive because both Wolf et al. and Arai et al. teach plasmid and viral vectors containing p53as as discussed supra. Further, both Wolf et al. and Arai et al. call for further study of p53as, and Lee et al. specifically teaches that insertion into baculovirus vectors facilitates further study of proteins by producing large quantities of protein. Further, Lee et al. teach the insertion of virtually any cDNA into the vectors with a reasonable expectation of success. Lee et al. does not specifically teach insertion of p53as cDNA, however, it is not necessary that the claimed invention be expressly suggested in any one or all of the references to justify combining their teachings; rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art *In re Keller,* 642 F.2d 413, 288 USPQ 871 9 CCPA 1981). Given the suggestion by Wolf et al. and Arai et al. to further study p53as and the teachings of Lee et al. that expression in baculovirus systems enhances study of new proteins, it would not involve hindsight, but rather would have been *prima facie* obvious to one of ordinary skill in the art to insert the cDNA of Wolf et al. or Arai et al. into the baculoviral system of Lee et al. with a reasonable expectation of success given the art standard technology of cloning into baculoviral vectors and taught by Lee et al. and one would be motivated to do so to obtain large quantities of protein for study as suggested by Lee et al. to be useful in the study of proteins which is suggested by both Wolf et al. and Arai et al.

11. Claims 1, 3, 4 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al (Nuc.Acids Res. 20:1979-1981, 1992), in view of Sambrook et al. Molecular Cloning, A laboratory Manual. Second Ed. Cold Spring Harbor Laboratory Press. 1989)

Han et al. teach as set forth in the Office Actions of 3/28/97, 10/15/98, and 2/10/99. Han et al. teach that existence of alternatively spliced RNA of p53, meeting the requirements of the instant p53as- i.e. C-terminal truncation of 9 amino acids and addition of 17 amino acids from Intron 10, is present in both normal and transformed cells and suggest that it's presence may be universal. See the abstract and page 1981. Indeed, the instant specification acknowledges the prior art knowledge of the existence of p53as and cites Han et al. Further, Han et al. use the art-known knowledge of the differences between p53as cDNA and other p53 species of cDNA to clone segments of p53as cDNA into plasmids and demonstrate the ubiquitous existence of p53as. Han et al. further provide primers and methods of determining the successful cloning of p53as cDNA product based on known C-terminal differences. Finally, Han et al. teach that more precise biochemical and biological characterization of p53as properties is critical in future studies of normal and oncogenic cells. See page 1981.

Han et al. differ from the instant invention by not teaching the cloning of full length p53as cDNA encoding p53as protein into plasmids. Applicant argues that this cloning is not obvious over Han et al. and would only be motivated by impermissible hindsight reconstruction from applicants own teachings. This is not found to be persuasive.

As stated in the previous Office Action of 2/10/99, cloning of cDNA into plasmids is art standard. Han et al. suggest that further study of wildtype p53as is necessary and that more precise biochemical and biological characterization of wildtype p53as properties are necessary.

Sambrook et al, a textbook of molecular cloning techniques, teach that expressing large amounts of proteins from cloned genes in plasmids was an art standard technique and known in the art to be invaluable to the purification, localization, and functional analysis of the proteins.

Thus, it would have been *prima facie* obvious to clone the DNA sequence encoding the p53as gene of Han et al. into a plasmid with a reasonable expectation of success using art standard technologies to obtain large amounts of expressed protein for further study, and one would have been motivated to do so because Han et al. suggest that further study of the p53as protein is needed. The cloning of DNA encoding p53as does not involve impermissible hindsight, but rather would have been obvious based on art standard knowledge.

12. Claims 5, 6, 8-11, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al (Nuc.Acids Res. 20:1979-1981, 1992), in view of Lee et al (IDS; EP 529160).

Han et al. teach as set forth above and in the Office Actions of 3/28/97, 10/15/98, and 2/10/99. Han et al. teach that existence of alternatively spliced RNA of p53, meeting the requirements of the instant p53as- i.e. C-terminal truncation of 9 amino acids and addition of 17 amino acids from Intron 10, is present in both normal and transformed cells and suggest that it's presence may be universal. See the abstract and page 1981. Indeed, the instant specification acknowledges the prior art knowledge of the existence of p53as and cites Han et al. Further, Han et al. use the art-known knowledge of the differences between p53as cDNA and other p53 species of cDNA to clone segments of p53as cDNA into plasmids and demonstrate the ubiquitous existence of p53as. Han et al. further provide primers and methods of determining the successful

cloning of p53as cDNA product based on known C-terminal differences. Finally, Han et al. teach that more precise biochemical and biological characterization of p53as properties is critical in future studies of normal and oncogenic cells. See page 1981.

Han et al. differ from the instant invention by not teaching the cloning of full length p53as cDNA encoding p53as protein into viral vectors. Applicant argues that this cloning is not obvious over Han et al. or Lee et al. and would only be motivated by impermissible hindsight reconstruction from applicants own teachings. This is not found to be persuasive.

Han et al. state that further study of wildtype p53as is necessary and that more precise biochemical and biological characterization of wildtype p53as properties are necessary.

Lee et al., as made of record in the Office Actions of 2/10/99 and 10/15/97 teaches the use of baculoviral vectors to produce large quantities of protein. Lee et al. teaches the importance of and the advantages of a mechanism to obtain intact, biochemically active protein in large quantities to advance investigation of the properties of that protein. (See page 2, lines 40-45). Lee et al. teach the cloning of cDNA into viral vectors to accomplish this advantage. Thus, not only does Lee et al. teach the technical feasibility of a reasonable expectation of success, Lee et al. also teaches a motivation to do so, i.e. to obtain large quantities of protein for investigation.

Lee et al. does not specifically teach insertion of p53as cDNA, however, it is not necessary that the claimed invention be expressly suggested in any one or all of the references to justify combining their teachings; rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art *In re Keller,* 642 F.2d 413, 288 USPQ

871 9 CCPA 1981). Given the suggestion by Han et al. to further study p53as and the teachings of Lee et al. that expression in baculovirus systems enhances study of new proteins, it would not involve hindsight, but rather would have been *prima facie* obvious to one of ordinary skill in the art to clone full length cDNA for p53as into baculovirus vectors with a reasonable expectation of success and one would have been motivated to do so to obtain large quantities of protein for further study which is suggested by Han et al. to be necessary.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvonne Eyler, Ph.D. whose telephone number is (703) 308-6564. The examiner can normally be reached on Monday through Friday from 830am to 630pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**paula.hutzell@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Yvonne Eyler
Yvonne Eyler
Patent Examiner

Yvonne Eyler, Ph.D.
July 30, 1999